AMENDMENTS TO THE DRAWINGS

Attached hereto is one (1) sheet of a replacement drawing that complies with the provisions of 37 C.F.R. § 1.83(a).

It is respectfully requested that the formal drawings be approved and made a part of the record of the above-identified application.

Attachment: Replacement sheet

AMENDMENTS TO THE SEQUENCE LISTING

IN THE SEQUENCE LISTING

Please replace the Sequence Listing of record with the Substitute Sequence Listing enclosed herewith.

REMARKS

The Office Action of December 30, 2006, presents the examination of claim 7, claims 1-6 and 8-26 being withdrawn pursuant to a Restriction Requirement.

Restrictions/Elections

Claims 1-6 and 8-26 stand withdrawn from consideration by the Examiner as being directed to a non-elected invention. Applicants request that rejoinder of at least claim 8 be considered once the present claim is allowed. Applicants submit that claim 8 represents a method of using the polypeptide of claim 7. Accordingly, should claim 7 be found allowable, at least claim 8 should be rejoined for examination and allowance, if commensurate in scope with claim 7. MPEP 821.04. Because claim 7 is believed to be allowable, Applicants request that the Examiner consider rejoinder of claim 8 at this time.

Information Disclosure Statement

The Examiner states that some of documents listed in the IDS filed February 9, 2004, have not been located. Applicants will file a supplemental IDS providing the documents, shortly hereafter for the Examiner's consideration.

Sequence Compliance

Enclosed herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a Substitute Sequence Listing to be inserted into the specification as indicated above. The Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a disk copy of the Substitute Sequence Listing. The disk copy of the Sequence Listing, file "2006-06-29 0933-0210P.ST25", **is identical to the paper copy**, except that it lacks formatting. The CRF and paper copy of the Sequence Listing **do not add new matter to the application.**

Drawings

The Examiner objects to Figure 6 because the Figure is allegedly too dark. Attached herewith is a replacement Figure 6 which complies with 37 CFR 1.83(a). Accordingly, Applicants request that the objection to Figure 6 be and withdrawn.

Specification

The Examiner objects to the term 'novel' in the title of the instant specification and the embedded hyperlinks on pages 6 and 20 of the instant specification. Additionally, the Examiner objects to a misspelling and a missing space on page 10. The hyperlinks are removed and the title is amended to remove the term "novel." Additionally, the misspelling is corrected and a space is added between the words "Cos-7" and "cells." Accordingly, Applicants request the objection be withdrawn.

Rejections under 35 U.S.C. § 101

Utility

Claim 7 is rejected under 35 U.S.C. § 101 as allegedly lacking utility. Applicants respectfully traverse.

The Examiner first asserts that the claimed invention is not supported by a specific utility. Particularly, the Examiner states that "Applicants' disclosure is to properties that are generic to essentially any protein", (Office Action, page 7). Applicants respectfully disagree.

The specification states that MANF2 protein is useful in treating neurologic disorders including central nervous system disorders, Parkinson's disease or Alzheimer's disease. Therefore, the specification clearly defines a use that depends upon the particular polypeptide

claimed. Thus, the utility is specific. (See, *e.g.* the Revised Interim Utility Guidelines Training Materials, 1999 (www.uspto.gov/web/offices/pac/utility/utilityguide.pdf) at Example 5, wherein the disclosed utility for a hypothetical protein is for "curing Alzheimer's." This utility is described as specific and substantial in the guidelines, although not credible.)

Second, the Examiner states that the asserted utility is not a "substantial" utility. However, since a treatment for Parkinson's disease is a desirable outcome based upon a need in the art, the disclosed use of the claimed protein is substantial and "real world." (See, Revised Interium Utility Guidelines Training Materials, at Example 5, *supra*).

In addition, the disclosed utility is credible, as well as specific and substantial. Applicants have derived the function of the instant MANF2, in part, on *in vitro* studies, which demonstrate that both human and mouse MANF2 promote survival of dopaminergic neurons as efficiently as human and mouse MANF1 *in vitro*. (page 8, line13-15 in the specification as filed). This disclosure strongly supports Applicants asserted utility.

The courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. The Federal Circuit, in *Cross v. Iizuka*, 753 F.2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985), commented on the significance of data from *in vitro* testing that showed pharmacological activity:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

Therefore Applicants submit that using the claim polypeptide, MANF2, for treating neurological diseases such as Parkinson's disease is specific, substantial and credible.

Additionally, Applicants submit that the claimed polypeptide, also, has a well-established utility as well as a specific, substantial and credible utility. Although the Examiner states that "the practice of assigning function based upon homology is highly unpredictable" and cites Smith and Zhang, (*Nature Biotechnology* 15: 1222-1223 ((1997)) and Tseng and Liang (Abstract, downloaded June 9, 2005) to support her contention, these references are not persuasive. The Applicants' assertion of the biological activity of MANF2 is supported because MANF1 and MANF2 share a high level of sequence similarity.

It is generally accepted in the art that proteins exhibiting a high degree of amino acid sequence similarity are likely to have similar physiologic function. The USPTO has agreed that "when two polynucleotides (polypeptides) show a high similarity to each other, it is probably that two polynucleotides (polypeptides) have any specific functions in common." (See, Trilateral Project B3b. Mutual Understanding in Search and Examination. Nucleic Acid Molecule-related inventions whose function is inferred based on homology search, Example 9. (www.trilateral.net/projects/biotechnology/mutual_understanding/mu_in_se.pdf) Additionally, this idea is embodied in the considerations for determining utility, in that it is accepted that structurally similar chemical compounds may credibly be asserted to have similar activities. *See,* MPEP § 2107.03.

Applicants submit that 79% sequence similarity is accepted by one of ordinary skill in the art as establishing likely identity of biological function and that this percent of similarity, as well as the fact that conserved alpha helices and eight cysteines are conserved between MANF1 and MANF2, is sufficient to establish, by a preponderance of the evidence that Applicants' asserted utility is true. *See, e.g. In re Oetiker*, 24 USPQ2d 1433 (Fed. Cir. 1992); *In re Caveney,* 226 USPQ 1 (Fed. Cir. 1985) and also MPEP § 2107.02. Moreover, the present specification shows that both MANF1 and MANF2 promote survival of dopaminergic cells *in vitro*. (See, *supra*).

Based on the discussion above, Applicants submit that the Examiner fails to establish any *prima facie* lack of utility of the claimed invention. Additionally, Applicants submit that even if a *prima facie* lack of utility is deemed established, the evidence of the data provided in the specification is sufficient to rebut such an assertion. Nevertheless, Applicants, additionally, provide herewith a Declaration under 1.132 wherein Applicants provide data, obtained according to Example 8 in the specification as filed, which further demonstrate that MANF2 has a specific, substantial, and credible utility for treating Parkinson's disease.

Parkinson's disease is a well-known disease characterized by a chronic and progressive motor disorder marked by the degeneration of dopaminergic neurons in the substantia nigra *pars compacta* (SNpc). Parkinson's is induced in animals by exposure to 6-hydroxydopamine (6-OHDA). The toxin results in brain pathology that mimics what is seen in human disease, that is, injections of the neurotoxin 6-hydroxydopamine (6-OHDA) into the rat dorsal striatum destroys the dopaminergic neurons in the *pars compacta* of the substantia nigra. Rescue of dopaminergic neurons after 6-OHDA by MANF2 is determined using behavioral tests and TH (tyrosine hydrolase) immunocytochemistry.

The data of the Saarma Declaration, which further support utility of the present invention, is described briefly, as follows. Applicants administered MANF2 or vehicle to rats, followed by the administration of 6-OHDA six hours later. (See, Saarma Declaration attached herewith for detailed experimental protocols). At two and four weeks post lesion, each rat was given D-amphetamine in order to induce ipsilateral (to the side of the lesion) turning behavior. At two weeks post lesion, D-amphetamine induced significant ipsilateral turning behavior in the group exposed only to vehicle and 6-OHDA (control group), but no increase in ipsilateral turns was observed in the group treated with MANF2 prior to 6-OHDA (treatment group).

At four weeks post lesion, the rats were sacrificed and tyrosine hydroxylase-positive cells (TH-positive cells) were counted in the SNpc in order to assess whether or not rescue of dopaminergic neurons after 6-OHDA by MANF2 occurred. The loss of TH-positive cells in the SNpc of the control group and the treatment group was 30% and 4%, respectively. Additionally, retrograde transport of MANF2 from the dorsal striatum to the substania nigra was observed. Thus, MANF2 can rescue midbrain domainergic neurons *in vivo* in the rat 6-OHDA model of Parkinson's disease. Therefore, MANF2, *inter alia*, has a utility as a therapeutic protein for the treatment of Parkinson's disease.

Rejections under 35 U.S.C. § 112, first pargraph

Enablement

Claim 7 is rejected under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement, *i.e.* of "how to use" the invention. The basis for this rejection is the same as that for the rejection under 35 U.S.C. § 101. This rejection is respectfully traversed.

The Examiner asserts that Applicants, solely on observations of sequence homology to MANF1, that MANF2 is useful for the treatment of neurological disorders. This allegation is untrue. Figures 11 and 12 of the instant specification show that MANF2, similarly to MANF1, promote survival of dopaminergic neurons. Therefore, there is adequate guidance in the specification to allow the skilled artisan to use the MANF1 polypeptide of claim 7.

The Examiner also asserts that the function of MANF2 has not been established. However, the instant specification, based on homology to MANF1, as well with *in vitro* studies, teaches the skilled artisan that MANF2 promotes the survival of dopaminergic neurons and, therefore, may be used to treat Parkinson's disease and other neurological diseases

The Examiner also states that predicting the function of proteins based on homology is an unpredictable art. Applicants submit that 79% sequence similarity is accepted by one of ordinary skill in the art as establishing likely identity of biological function. Moreover, the *in vitro* studies of MANF1, described *supra,* support that contention that even if ascribing function based on *in silico* methods were unpredictable, there is adequate guidance in the specification to teach a skilled artisan how to use the present invention. Furthermore, the Saarma Declaration, described above, demonstrates that a person of skill in the art is adequately guided by the specification to understand how to use the claimed polypeptide, *inter alia*, to treat Parkinson's disease.

Accordingly, Applicants respectfully request the rejection be reconsidered and withdrawn.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to the undersigned at the telephone number of below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: JUN 30 2006

Respectfully submitted,

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Attachments